

LECTURE PRESENTATION

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Structure-function relationship of γ -secretase

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From 2011 International Conference on Molecular Neurodegeneration
Shanghai, China. 22-24 September 2011

Background

Genetic and biological studies provide strong evidence that the production and deposition of amyloid- β peptides ($A\beta$) contribute to the etiology of Alzheimer's disease (AD). γ -Secretase is an unusual aspartic protease that cleaves the scissile bond within the transmembrane domain of APP to generate $A\beta$. This unusual enzyme is composed of a high molecular weight membrane protein complex containing presenilin, nicastrin, Aph-1 and Pen-2. Drugs that regulate the production of $A\beta$ by inhibiting or modulating the γ -secretase activity could provide a disease-modifying effect on AD, although recent studies suggest that the γ -secretase plays important roles in cellular signaling including Notch pathway. Thus, understanding the molecular mechanism whereby the γ -secretase cleaves its substrate is a critical issue for the development of compounds that specifically regulate the $A\beta$ -generating γ -secretase activity.

Methods

To analyze the structure of PS, the catalytic subunit of γ -secretase, we have employed substituted cysteine accessibility method (SCAM), a biochemical method by which structures of various membrane proteins have been analyzed in a functional state. In addition, we identified the target molecule/domain of the γ -secretase inhibitors and modulators using chemical biology approach. Finally, we rationally developed novel reagents that regulate the γ -secretase activity.

Results

We found that the hydrophilic "catalytic pore" structure of γ -secretase is formed by the transmembrane domains (TMD) 1, 6, 7 and 9 of PS1 within the membrane. Competition experiments by γ -secretase inhibitors suggest that the N-terminal region of TMD1 directly faces the hydrophilic environment within the lipid bilayer as a part of the

catalytic site. Intriguingly, inhibitor binding affected water accessibility of residues at the membrane border of TMD1. Moreover, we successfully raised a novel inhibitory monoclonal antibody against γ -secretase activity, which targets the juxtamembrane region of TMD1 of PS1. Finally, we identified that GSM-1, a potent γ -secretase modulator, binds to the hydrophobic region of TMD1 and affects the catalytic pore structure.

Conclusion

TMD1 of PS1 is a functionally critical domain for the γ -secretase activity.

Published: 7 February 2012

doi:10.1186/1750-1326-7-S1-L5

Cite this article as: Tomita: Structure-function relationship of γ -secretase. *Molecular Neurodegeneration* 2012 **7**(Suppl 1):L5.

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